

Blood circulation infections and empirical treatment approach in hemodialysis patients

Catheter-related bacteraemia in hemodialysis

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Abstract

Aim: Catheter infection is an important complication of hemodialysis that may cause sepsis and death. In our study, it was aimed to analyze the catheter and blood culture results of patients who underwent hemodialysis due to chronic kidney failure.

Materials and Methods: In a special dialysis center providing ambulatory hemodialysis service, 1202 patients with chronic renal failure who underwent hemodialysis between January 2017 and June 2019 were included in the study. At least one hemodialysis catheter lumen and simultaneous peripheral blood culture were taken from patients with the suspicion of catheter-related bloodstream infection. In 95 of the patients, 115 catheter-related bloodstream infections attacks were detected. The results were evaluated retrospectively.

Results: Gram-positive and Gram-negative bacteria were grown in 66.1% and 33.9%, respectively. The most frequent microorganisms were coagulase-negative staphylococci (42.7%), *Staphylococcus aureus* (14.5%), and *Enterobacter cloacae* (13.7%). A total of 38.9% of the *S. aureus* isolates were resistant to methicillin. All of the *E. cloacae* isolates were susceptible to high levels of aminoglycosis, carbapenems, colistin, and tigecycline. The detection rate of polymicrobial bacteraemia was 8.6%.

Discussion: Our study was one of the rare studies investigating catheter-induced bacteraemia cases and a possible Gram-negative bacterial outbreak in hemodialysis patients. We consider that the data of our study about the microorganisms in hemodialysis catheter-related bacteraemia cases will be informative to clinicians and researchers, and it will be remarkable for taking measures to protect hemodialysis patients against possible outbreaks.

Keywords

Hemodialysis, Catheter infection, Bacteraemia

DOI: 10.4328/ACAM.20246 Received: 2020-06-12 Accepted: 2020-07-17 Published Online: 2020-07-27 Printed: 2020-11-01 Ann Clin Anal Med 2020;11(6):563-567

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Introduction

Renal replacement therapies are life-saving for patients with chronic renal failure. Renal replacement treatments include continuous ambulatory peritoneal dialysis, kidney transplant, and the most preferred method, hemodialysis. In our country, tens of thousands of patients per year, and hundreds of thousands of patients worldwide, are regularly undergoing hemodialysis. Hemodialysis treatment is most often performed through the arteriovenous fistula (AV fistula), which has the best persistence and has the lowest vascular access routes with mortality and morbidity. It is necessary to wait 3-4 weeks of ripening period before AV fistula can be opened. If AV fistula cannot mature for a variety of reasons until AV-fistula cannot be opened, hemodialysis treatments are provided with temporary and permanent hemodialysis catheters. Various complications can develop due to this method in the patients who have undergone haemodialysis using a catheter [1-3]. The most common complications are central catheter-related bloodstream infections, which is a healthcare-related infection, and these bacteraemias may progress to infective endocarditis and serious infections that may eventually result in death. [4-8]. Gram-positive bacteria are the most common factors in central catheter-related bloodstream infections in hemodialysis patients. Gram-negative bacteria are less frequent, but their treatment is more difficult than Gram-positive, and often requires catheter withdrawal or change. Depending on the bacterial factors, different patients in the same clinic, in a certain period of time, and identifying the same factor appear as an epidemic. This is when the same bacteria are transmitted to other patients. Thus, patients without any infection will be affected by the transmitted factor, and their general condition will deteriorate faster [9-11].

In hemodialysis patients, catheter-related bloodstream infections are difficult to treat, and they prolong hospital stay and reduce patient quality of life. If catheter-related sepsis is not treated early and accurately, it can cause high mortality and morbidity. However, it may be life-saving if the clinician starts appropriate antimicrobial treatment on time [1,2,7,8]. To do this, first of all, the identification of the microorganism causing the catheter-related circulation infection should be done immediately and accurately and should be reported to the clinician. During this period, in order for the patients to receive appropriate empirical treatment, each center should have information about the presence of the microorganisms in these patients in their region. For this reason, each center should follow the factors and their susceptibility in hemodialysis patients periodically.

In our study, it was aimed to analyze the microorganisms causing catheter-related bloodstream infection developing in patients undergoing hemodialysis due to chronic renal failure, and to determine empirical treatment options in these patients.

Material and Methods

This study has been approved by the local ethics committee.

Patients and Tests

A total of 1202 patients who admitted to the outpatient hemodialysis center between January 2017 and June 2019 were included in the study. Patients with at least one of the

hemodialysis catheter lumens and simultaneous peripheral venous blood cultures were evaluated with suspicion of central catheter-related bloodstream infection. Appropriate catheter and blood culture samples, placed in a fully automated blood culture bottle, Bact/Alert 3D (BioMérieux, France), were transferred to the microbiology laboratory. When a positive signal was received from the device, indicating that the microorganisms were detected, specimens were taken from the bottles and were inoculated onto 5% sheep blood agar and eosin methylene blue media (Salubris, Turkey), and incubated. Colonies grown on the media were identified by a fully automated system (Vitek® 2 Compact, BioMérieux, France) after incubation. Staining slides were also prepared from the swab samples (Gül Biology, Turkey). In the microscopic examination of Gram staining, microbiological structures observed at 100 x magnification were recorded.

Statistical analysis

All statistical analyzes in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as numbers and percentages.

Results

Among the patients included in the study, 54 (56.8%) were male and 41 (43.2%) were female. The mean age was 62.2 ± 13.7 years in male patients, and 65.3 ± 11.6 years in female patients. In 95 of the patients, 115 catheter-related bloodstream infection attacks were detected. Catheter infection attacks developed in 14 of 95 patients twice, and in three patients three times.

Gram-positive bacteria were grown in 66.1% of blood cultures, and Gram-negative bacteria were grown in 33.8%. The most frequent microorganisms were coagulase-negative staphylococci (42.7%), *Staphylococcus aureus* (14.5%) and *Enterobacter cloacae* (13.7%) (Table 1).

A total of 85.9% of coagulase-negative staphylococci grown in the cultures were resistant to penicillin, and 75.5% to methicillin. A total of 61.1% of the *S. aureus* isolates were resistant to penicillin, and 38.9% to methicillin (Table 2). Among the coagulase-negative staphylococcus group (n:53), the most frequent species were *S. epidermidis* 45 (84.8%). Others types of Coagulase-negative staphylococci were *S. haemolyticus* 3 (5,6%), *S. hominis* 3 (5,6%), *S. liquefaciens* 1 (2%), *S. sciuri* 1 (%2). All of the *E. cloacae* isolates were susceptible to high levels of aminoglycosides, carbapenems, colistin, and tigecycline (Table 3). The polymicrobial bacteraemia rate was 8.6%.

Discussion

It is known that the development of health-related central venous catheter-related bloodstream infection in patients who need to undergo hemodialysis regularly due to chronic kidney failure is a common complication. It is of vital importance to diagnose catheter-related bacteraemia early and accurately. Rapid and appropriate treatment of this infection will reduce mortality and morbidity. Therefore, causative microorganisms should be monitored by each center. As it is known, microorganisms of the skin flora are frequently grown in blood cultures due to catheter colonization. However, risk factors may vary depending on the patient, hospital, and region where the research is conducted.

Table 1. Distribution of microorganisms reproducing according to culture results

Causative microorganism	n
Gram-positive bacteria	82
Coagulase-negative staphylococci	53
Staphylococcus aureus	18
Enterococcus faecalis	6
Diphtheroid bacilli	3
Streptococcus agalactiae	1
Streptococcus mitis/oralis	1
Gram-negative bacteria	42
Enterobacter cloacae	17
Klebsiella pneumoniae	6
Pseudomonas aeruginosa	5
Stenotrophomonas maltophilia	3
Serratia marcescens	2
Escherichia coli	2
Enterobacter aerogenes	2
Acinetobacter baumannii	2
Klebsiella oxytoca	1
Citrobacter koseri	1
Cronobacter sakazakii	1

Table 2. Distribution of staphylococci growing in cultures according to penicillin and methicillin resistance

	Penicillin resistance		Meticillin resistance	
	n	%	n	%
Staphylococcus spp. (n=71)	61	85.9	47	66.2
Coagulase-negative staphylococci (n=53)	50	94.3	40	56.3
S. aureus (n=18)	11	61.11	7	9.9

Table 3. Distribution of Gram-negative bacteria in terms of antibiotic susceptibility rates

	n	AN n (%)	CRO n (%)	CAZ n (%)	ERT n (%)	ME n (%)	CIP n (%)	C n (%)
Enterobacter cloacae	17	17 (100)	14 (82.4)	14 (82.4)	17 (100)	17 (100)	17 (100)	17 (100)
Klebsiella pneumoniae	6	5 (83.3)	3 (50)	3 (50)	5 (83.3)	5 (83.3)	5 (83.3)	6 (100)
Pseudomonas aeruginosa	5	5 (100)	-	5 (100)	-	5 (100)	5 (100)	5 (%100)
Stenotrophomonas maltophilia	3	-	-	-	-	-	3 (100)	-
Serratia marcescens	2	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)
Escherichia coli	2	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	1 (50)	2 (100)
Enterobacter aerogenes	2	2 (100)	1 (50)	1 (50)	2 (100)	2 (100)	1 (50)	2 (100)
Acinetobacter baumannii	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
Klebsiella oxytoca	1	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	-
Citrobacter koseri	1	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	-
Cronobacter sakazakii	1	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	-

AN: Aminoglycoside, CRO: Ceftriaxone, JAZZ: Ceftazidime, ERT: Ertapenem, ME: Meropenem, CIP: Ciprofloxacin, CT: Colistin.

Therefore, knowing the distribution of blood culture results of such cases in different regions provides information on the management of the infection [5-8].

It is expected that Gram-positive bacteria growth, especially including skin flora microorganisms, will be seen in bloodstream infections caused by hemodialysis catheter. Accordingly, bacteria in the skin flora often colonize the catheter, and pass to the bloodstream [2-5]. Quittnat Pelletier et al. [9] reported that Gram-positive bacteria were grown in 74.1% of 178 hemodialysis catheter-related bloodstream infection cases, and that the most common bacteria were *S. aureus* (34.5%), *Serratia marcescens* (17.2%) and coagulase-negative staphylococci (11.2%). Sahli et al. [10] reported the Gram-positive bacterial growth rate as 18.1% in their study conducted with 94 hemodialysis patients. Alexandraki et al. [11] found that the Gram-positive rate was 55% in their study conducted with 153 blood cultures. Similar to these studies, Saeed et al. [12], Nabi et al. [13], Lemaire et al. [14], Mattous et al. [15], Sanavi et al. [16], Tanrıöver et al. [17], Engemann et al. [18] and del Pozo et al. [19] reported that the most common cause of catheter-induced bacteraemia was *S. aureus* in their studies with hemodialysis patients. Similar to these reports, the most common factors were Gram-positive bacteria (66.1%) in the present study, and *S. aureus* rate was 14.5% and coagulase-negative staphylococcus was 42.7%. These data show that Gram-positive bacteria in the skin flora account for the major rate in the hemodialysis catheter-related bacteraemia cases.

In hemodialysis patients, it is also possible that the causative microorganism is a Gram-negative bacterium in catheter-related bloodstream infection cases. However, the detection of a Gram-negative bacterium at a higher frequency than expected may suggest an outbreak in that center [9-11]. Quittnat Pelletier et al. [9] reported that *Serratia marcescens*, a Gram-negative species, were detected in 17.2% of the cases. Pop-Vicaz et al. [20] reported that 9.0% of 67 hemodialysis catheter-induced bacteraemia cases had *Stenotrophomonas* growth. Sahli et al. [10] reported that *Klebsiella pneumoniae* was detected in 9.6% of patients in their studies involving the same type of cases. Alexandraki et al. [11] reported that the most frequent Gram-negative bacteria were *Enterobacter* species with a rate of 18.7%. In our study, *E. cloacae* was found with a rate of 13.7%. The rates of *Stenotrophomonas*, *Klebsiella*, *Serratia* and *Enterobacter* reported in all these studies are far above the expected rates in blood cultures with the diagnosis of catheter-related bloodstream infection. This condition suggests a possible epidemic caused by Gram-negative bacteria in all these studies. However, Alexandraki et al. [11] emphasized that the high *Enterobacter* ratio reached an alarming level in their study covering over a five-year period. However, in our study, an outbreak analysis and molecular tests were not applied to *Enterobacter* strains, and no epidemic investigations were performed.

The development of Gram-negative bacteraemia in a hemodialysis patient is explained by two following mechanisms: (i) exogenous transmission pathway from patient to patient through healthcare professionals or environmental factors; and (ii) endogenous transmission pathway through the passage of intestinal flora [20,21]. It has been stated in the endogenous

transmission pathway that Gram-negative bacteria in the large intestine can be translocated from the intestinal wall into the bloodstream or fecal contamination of vascular devices [20,22]. Therefore, it has been emphasized that the patient colonized with a Gram-negative bacterium is at high risk for bacteraemia caused by that bacterium [20]. Pop-Vicaz et al. [20] reported that 69% of their patients were infected endogenously. The exogenous road mentioned above is the expected source of outbreaks in health centers. Ben-Ami et al. [23] reported that 15% of patients colonized by Gram-negative bacteria developed bacteraemia caused by the same bacteria. The high rate of bacteraemia cases caused by the bacteria of the Enterobacteriaceae family in our study supports this data.

Pop-Vicaz et al. [20] stated that Gram-negative bacteria that they detected in hemodialysis patients who developed bacteraemia were multi-drug resistant. Sahli et al. [10] also emphasized that Gram-negative bacteria detected in their studies had high resistance rates. However, isolates of the Enterobacteriaceae family detected in our study were mostly susceptible strains without multiple drug resistance.

Given the causative microorganisms in the study and their susceptibility patterns, glycopeptide treatment such as vancomycin should be planned to cover methicillin-resistant staphylococci in empirical treatment. In severe clinical manifestations such as sepsis, ceftriaxone or ceftazidime, one of the third generation cephalosporins, should also be included in empirical treatment to cover the Gram-negative bacteria. Each hemodialysis center or institution following these patients should monitor the distribution of causative microorganisms and resistance patterns. Thus, the optimal empirical treatment option to be started in patients can be determined [1-4].

Hemodialysis catheter-related bacteraemia cases are frequently polymicrobial. In these cases, various bacteria can cause bacteraemia together. Widespread use of vancomycin, regular and long-term hemodialysis, and regular antiseptic application to the catheter outlet are among the causes of polymicrobial bacteraemia [11,24]. Alexandraki et al. [11] reported the polymicrobial bacteraemia rate as high as 28.1%. In our study, the polymicrobial bacteraemia rate was 8.6%.

Quittnat-Pelletier et al. [9] detected no fungal growth in their studies. Sahli et al. [10] reported that only two of their patients had fungal growth. Alexandraki et al. [11] also detected fungus in only one patient. In our study, no fungal growth was observed. These data support that fungal growth is not expected frequently in hemodialysis catheter-related bacteraemia cases. The most important limitation of this study was that some data such as the date of insertion, the location of the hemodialysis catheter and the withdrawal date after the catheter infection could not be accessed because only blood cultures of the patients were performed in the microbiology laboratory. In addition, information that the hemodialysis catheter had a temporary/permanent feature could not be accessed due to the same reason. It was also unknown whether there was a colonization or carrier status for the healthcare workers at that period. Apart from this, one limitation in our study was that a molecular test such as pulsed-field gel electrophoresis or polymerized chain reaction was not performed to the isolates in the microbiology laboratory, and the possible clonal relationship

between the isolates could not be determined. For this reason, it could not be proven whether there was an outbreak.

It is critical to protect hemodialysis patients against complications, especially catheter-related infections. Protecting patients, especially against an outbreak caused by Gram-negative bacteria, can be life-saving. Our study is one of the rare studies investigating catheter-induced bacteraemia cases and a possible Gram negative bacterial outbreak in hemodialysis patients. We consider that the data of our study will be informative to clinicians and researchers about the microorganisms in hemodialysis catheter-related bacteraemia cases, and it will be remarkable in order to take measures to protect hemodialysis patients against possible outbreaks.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Derya Bayirli Turan. Blood circulation infections and empirical treatment approach in hemodialysis patients. *Ann Clin Anal Med* 2020;11(6):563-567